Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 7349–7353, October 1987
Psychology

Deficits in human visual spatial attention following thalamic lesions

(selective attention)

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Contributed by Michael I. Posner, June 29, 1987

ABSTRACT **There has been speculation concerning the role that thalamic nuclei play in directing attention to locations in visual space [Crick, F. (1984) *Proc. Natl. Acad. Sci. USA* 81, 4586–4590]. We measured covert shifts of visual attention in three patients with unilateral thalamic hemorrhages shortly after the lesion and after a 6-month recovery period. The experiment measured reaction time to targets that occurred at locations to which attention had been cued (valid trials) or at a currently unattended location (invalid trials). Although the patients showed no deficits in visual fields with perimetry and no neglect in the 6-month follow-up, we found slow reaction times for targets on the side contralateral to the lesion whether or not attention had been cued to that location. Deficits have also been found in this task with cortical and midbrain lesions, but the patterns of performance are quite different. The results with thalamic patients suggest they have a specific deficit in the ability to use attention to improve the efficiency of processing visual targets contralateral to the lesion (engage operation). This finding is in accord with hypotheses of a thalamic link between cortical visual attention and pattern recognition systems proposed by Crick.**

A number of specific experimental methods have been used with alert monkeys (1–3) and humans (4–6) that force covert shifts of attention following closely in the time after the presentation of cues. In neurophysiological studies the orientation of attention is inferred from selective enhancement in neuron firing rate in response to the cue. Cognitive studies measure the allocation of attention in terms of improved efficiency in responding to signals at the cued locations in comparison to other spatial locations. These approaches have begun to converge to identify the neural mechanisms controlling visual attention. Cognitive studies with normal humans using visual cues to direct attention covertly to a location eccentric from the point of fixation show more efficient processing of signals at the cued location. This enhancement includes lowered manual (5) and saccadic (7) reaction times, reduced sensory thresholds (8), improvement in conjoining features (9), and modulation of evoked electrical potentials recorded from the scalp.§ These observations support the concept of attention as a mechanism for relative enhancement of information processing at a selected spatial location. There is also evidence that the area of enhancement becomes larger as cues are presented more eccentrically in correspondence with the known characteristics of the neural magnification factor (10, 11).

Areas of the monkey brain showing selective neuronal enhancement include the posterior parietal lobe (1, 2), the superior colliculus (2) and substantia nigra (pr) (12) of the midbrain, and the lateral pulvinar (13). The same visual cueing method described above was used to demonstrate that modulation of neurotransmission by γ-aminobutyric acid (GABAergic transmission) in thalamus (with iontophoretic injections of muscimol or bicuculline) systematically affects the orientation of attention contralaterally (14). Reaction-time studies using cueing in neurologic patients have confirmed that lesions of the parietal lobe (15) and peritectal regions of the midbrain (16) produce distinctly different deficits in orienting visual attention.

Three computations have been suggested in the orientation of visual attention. First, attention must "disengage" from the current location; then "move" to a new location; then "engage" at the new location. Deficits in each of these three elementary operations can be identified in cueing studies. At the beginning of the trial the subject is maintaining fixation at the center of the display without actively attending to any spatial position (no targets occur at the center). When the cue is presented, the subject must move attention to the cued location and engage attention there in anticipation of the forthcoming target. The efficiency of moving attention can be inferred, then, from the rate of improvement of reaction time with cue-to-target delay on valid trials. A deficit in the move operation can be inferred by a deficiency (i.e., a delay or reduction) in this improvement.

A deficit in the move operation has been found in patients with progressive supranuclear palsy who have degeneration of the superior colliculus and peritectal region (16). In these patients saccadic eye movements are relatively more impaired in the vertical dimension than are horizontal eye movements. We, therefore, compared vertical and horizontal attention shifts. Reaction time on valid trials improved more slowly with time following the cue in the vertical dimension.

A different pattern of results was shown for patients with parietal lesions (15). Reaction times improved at the same rate in both visual fields following a valid cue. This indicates that parietal lesions do not slow the movement of attention toward the contralateral field. Moreover, the asymptote of these functions differed very little between fields showing that the ability to use attention to engage the target location did not differ greatly between visual fields. In contrast to the midbrain patients, there was a dramatic increase in reaction times to targets in the contralateral field following invalid cues. According to our scheme, if attention is shifted to the cue but the target appears elsewhere, it is necessary to disengage attention from the cue before moving to the target. The selective slowing of detection reaction time in the invalid cue condition suggests, therefore, that the parietal lobe plays a special role in mediating the disengage operation.

Parietal lesions and midbrain lesions have distinctly different effects on orienting attention: midbrain lesions appear to produce a specific deficit in the move operation, whereas

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Abbreviation: CT, computerized tomography.

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§Mangun, G. R., Hansen, J. C. & Hillyard, S. A., Proceedings of the Eighth International Conference on Event Related Potentials, June 1986, Stanford, CA, ONR Tech. Rep. SDEPL 001.

parietal lesions selectively appear to produce a specific deficit in the disengage operation.

We now extend the use of cueing paradigms to measure attention shifts in three neurological patients with thalamic hemorrhages. This method permits us to compare the thalamic deficit with those found in midbrain and parietal patients. Lesions of any of these areas can produce clinical symptoms of neglect of contralateral stimuli (17). However, the computations performed by these areas may be quite different. If the patterns of performance deficit due to lesions of these areas differ, it should be possible to further the analysis of the role of each area.

METHODS

Subjects. Three patients with hemorrhages in the thalamus were studied in an experiment to measure covert shifts of visual attention on two occasions: in the acute stage they were tested as soon as they were able to perform the task; each was retested after 4–6 months of recovery (chronic stage). Patient VM, a 65-year-old man, had a large hemorrhage centered in the left thalamus with rupture of the hemorrhage into the ventricular system. He was initially comatose with right hemiplegia, hemianesthesia, and ocular skew deviation. Fig. 1 shows the computerized tomography (CT) scan findings at the time of his initial testing, 7 weeks after the ictus. At that time he still manifested some psychomotor retardation and mild visual neglect. At the time of retesting 6 months after the ictus, he was alert, lucid, and subtle visual neglect was evident only on a letter cancellation task. The other two patients had smaller lesions that did not impair alertness and were first tested in the second week of their illness. Patient VL, a 67-year-old woman, had a hematoma in the right thalamus (Fig. 2). Patient NA, a 54-year-old man, had a small hematoma in the right thalamus involving the nuclei centromedianum, ventrolateral, and lateral posterior (Fig. 3 *Upper*). The hemorrhage extended into the posterior limb of the internal capsule and ventral to the thalamus into the region of the zona incerta and perigeniculate region (Fig. 3 *Lower*). [Localization of the lesions was determined by relating the CT findings to De Armond *et al.* (18).] Patients VA and NL had hemiparesis and hemisensory impairment contralateral to their lesions. Neither had any signs of visual neglect (neglect is defined as a difficulty in reporting stimuli contralateral to the lesion without any sensory deficit) on detailed clinical testing. At the time of follow-up testing 4–6 months after their strokes, perimetry testing confirmed that the visual fields were intact in all three patients.

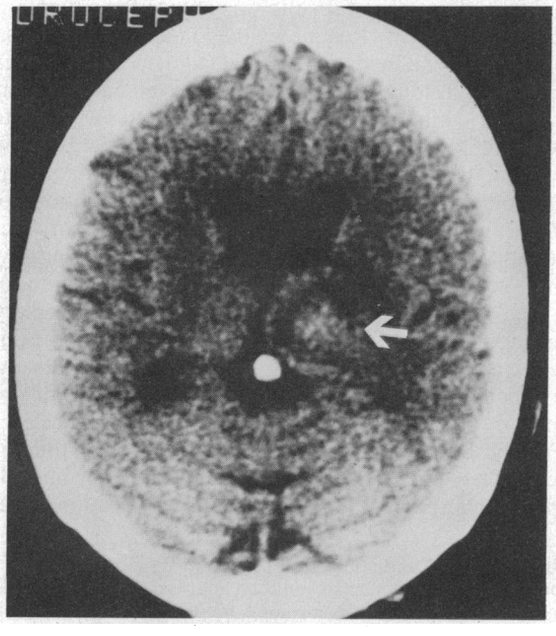

FIG. 1. CT scan from patient VM at the time of acute-phase testing 7 weeks after his stroke. There is a resolving large hematoma (arrow) centered in the left pulvinar.

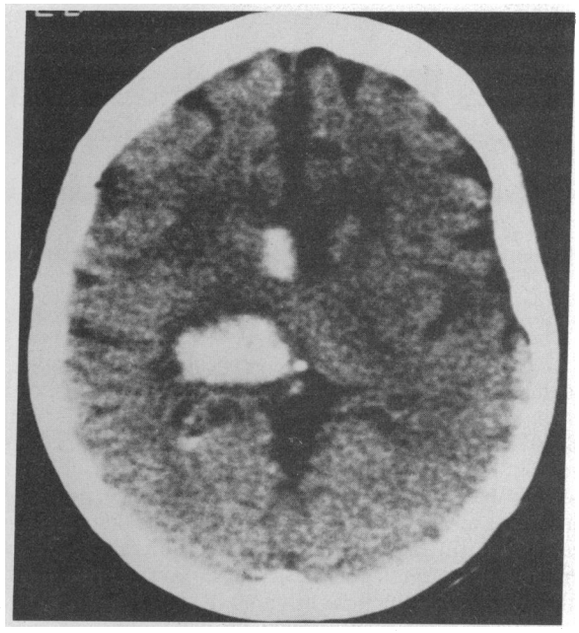

FIG. 2. CT scan from patient VL at the time of her stroke showing a large hematoma (large white area) in the posterior right thalamus (small white area is blood in the lateral ventricle).

Procedure. Subjects sat facing a video display screen with one finger of the preferred hand on a response key placed on a table between the subject and the display. Light pressure on the key activated a microswitch that recorded reaction time. The display consisted of a (+) sign at the center, flanked 5° to left and right by a 1° unfilled square. Subjects were instructed to maintain gaze on a (+) sign in the middle of the screen and not to move the eyes. Eye position was monitored with a closed circuit video camera to assure that the eyes remained fixed at the center. Subjects practiced the task before data were collected while the experimenter observed to ascertain that the directions were understood and that the subject was not moving the eyes. The intertrial interval was 2 sec. At the start of each trial the fixation point was extinguished, and 0.5 sec later the cue was presented by brightening, randomly and with equal probability, one of the two peripheral boxes. The cue remained visible for 300 msec. After an interval (50, 150, 500, or 1000 msec) following the onset of the cue, a target appeared either at the cued location or in the opposite visual field. Subjects were instructed to press the response key as quickly as possible any time the target (a bright asterisk filling one of the peripheral boxes) appeared. The target remained visible until the subject responded (or for 5000 msec). In this experiment, the target was on the cued side in 80% of trials (valid trials), whereas in 20% of trials, the target appeared in the box contralateral to the cue. The probabilities were designed to induce the shift and maintenance of attention to the cued location. Since the eyes remained fixed at the center and since the motor response (a simple key press) was always the same, any difference of reaction time between valid and invalid cue conditions may be assumed to index a covert movement of attention to the cued location.

RESULTS

We first excluded all reaction times <100 or >4000 msec. Only a few times were affected by this rule. The median

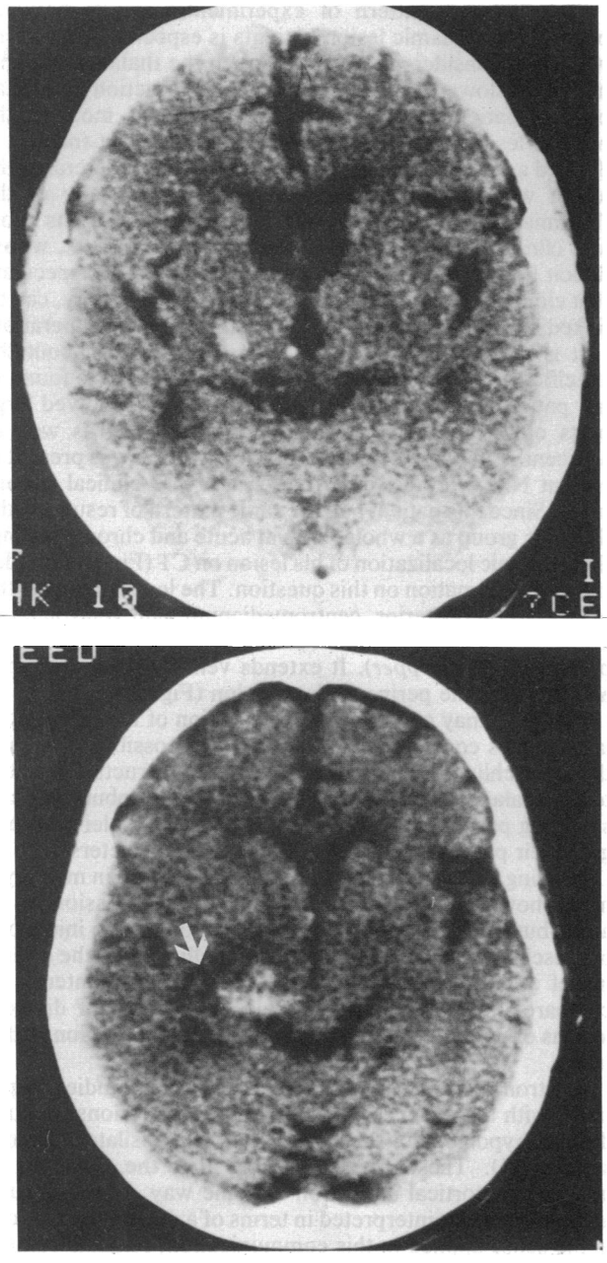

FIG. 3. CT scan from patient NA at the time of his stroke. (*Upper*) There is a small hematoma in the right thalamus centered in the ventrolateral nucleus and involving nuclei lateral posterior and centromedianum. (*Lower*) The hematoma extends into the posterior limb of the interanal capsule and ventral to the thalamus into the area of the zona incerta and into the perigeniculate region (arrow).

reaction time for each patient in each condition was calculated.

A within-factor analysis of variance was run with the following factors: stage of illness (acute vs. 6-month follow-up), target field (contralateral to lesion vs. ipsilateral to lesion), cue validity [target appeared at cued location (valid) vs. at uncued location (invalid)], and cue-to-target interval (50, 150, 550, or 1000 msec.).

When tested in the chronic stage (6 months or more after the lesion) the patients were faster than in the acute stage but this did not reach statistical significance ($F[1,2] = 2.65$). Thus, we display the combined data for acute and chronic tests in Fig. 4.

Reaction times are faster in the ipsilateral field than in the contralateral field for both validity conditions ($F[1,2] = 36.8$, $P < 0.025$). Validity (reaction time to targets at uncued location versus reaction time to targets at cued locations) has a significant effect with valid targets (solid lines) responded to faster than invalid targets (dashed lines) ($F[1,2] = 23$, $P < 0.05$), and validity interacts with the interval such that its effects are greater at short cue-to-target intervals ($F[3,6] = 8$, $P < 0.025$). Finally, this interaction of the validity and interval is significantly greater in the contralateral visual field than in the ipsilateral field, resulting in a triple-order interaction between validity, field, and interval ($F[3,6] = 11$, $P < 0.01$).

These results would be consistent with a primary visual defect in our patients. However, our thalamic patients had no clinical evidence of visual impairment, and, as mentioned, clinical neglect was not conspicuous (and was totally absent in two of the patients). All three patients showed no contralateral visual field defect on formal perimetric examination, even with the smallest (3-mm) target. Since the target in our experiment was a large (1°), bright signal presented in the parafoveal (5° eccentricity) region, it seems very unlikely that a subtle visual-field defect, beyond the sensitivity of perimetric testing, could have accounted for the dramatic slowing of contralesional detection reaction time. A fourth patient with a posterior cerebral artery stroke syndrome and CT evidence of infarction in the right thalamus and occipital lobe was also tested. He had a dense homonymous hemianopia and could not respond to any signal presented in this contralesional visual field. He was tested in an experiment where all cues and targets were presented in his intact visual field ipsilateral to the lesion (19). The target was presented at the same location on each trial but was preceded by a cue that first summoned attention either to the left or right of the forthcoming target. On each trial, then, he had to disengage his attention to move it in either an ipsilesional or contralesional direction. When he had to shift attention leftward (contralesionally), detection reaction times were systematically longer than when he had to shift attention rightward (ipsilesionally). This result, obtained entirely within the intact visual field, could not have been due to differences in

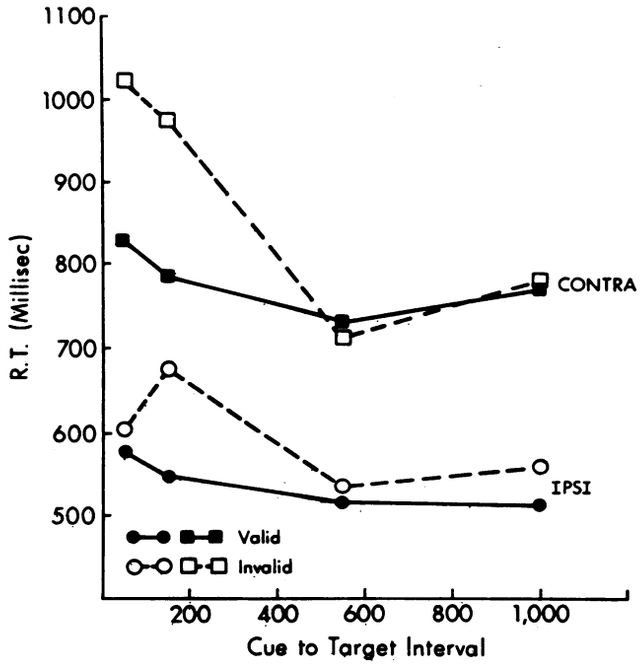

FIG. 4. Mean reaction time for three thalamic patients as a function of cue-to-target interval (stimulus onset asynchrony). Contra, contralateral; ipsi, ipsilateral.

visual sensitivity since the target always occurred at the same location.

DISCUSSION

There are three salient features of the data depicted in Fig. 4. (*i*) For the valid trials, the cue produces a similar improvement in reaction time, as a function of cue-to-target interval, in both visual fields. (*ii*) For the invalid trials, there are slow reaction times in the contralesional field for the short cue-to-target intervals. (*iii*) There is a dramatic main effect of visual field, with mean reaction time to contralesional targets being substantially slower. Consideration of these three findings in comparison to previous findings for patients with midbrain and parietal lobe lesions provides insights into the role of the thalamus in a distributed neural system for orienting visual attention.

Inspection of the data from the valid cue condition reveals a decrease in reaction time with interval. Although reaction time is slower for all contralesional targets, the improvement in reaction time from valid cues over time is equivalent in the two hemifields. This pattern for valid cue trials differs from what we have found in patients with midbrain lesions in whom we have argued for a disorder in the move operation. In midbrain patients the improvement of reaction time on valid trials was slower in the affected direction (vertical). Thus, midbrain patients were slow in moving attention. In contrast, for the thalamic subjects, reaction time to valid trials improves following the cue with a similar time course in both visual fields. In contrast to the midbrain lesion patients, they do not appear to have a deficit in moving attention in response to cues.

The second feature of these results is the long reaction times on the invalid trials relative to valid trials in the contralesional field for the short cue-to-target intervals. This pattern is similar to that found in our parietal patients and suggests that thalamic lesions affect the disengage operation in a qualitatively similar way. Indeed, the mean reaction time to invalidly cued contralesional targets for these early cue-to-target intervals in the thalamic lesion patients is similar to that previously identified for patients with right parietal lesions. Nevertheless, the relative slowing on invalid trials when compared to validly cued targets in the same field is much less in the thalamic patients. Moreover, the disengage deficit in the parietal lesion patients persisted even through the longest (1000 msec) cue-to-target interval. In the thalamic lesion patients, the disengage deficit is manifest only at the early cue-to-target intervals, while the cue is still present. We conclude that, although intact thalamic function may be necessary for disengaging attention, the parietal lobe is chiefly responsible for this operation. The thalamic lesion may have an indirect effect on parietal function to produce the disengage deficit.

In spite of their apparent ability to move their attention in response to the cue, the third and most striking aspect of the data is the persisting main effect of visual field for both valid and invalid targets. Even at the 1000-msec cue-to-target interval, when attention has had time to reach the target location, reaction time to detect contralesional targets remains slower and at no time is this difference <200 msec. This difference between the two visual fields is about four times as long as the mean difference that we found for parietal lesion patients (15). Only one of those 13 parietal patients showed a reaction time for validly cued contralateral targets at the 1000-msec cue-to-target interval that was as long as the mean for the three thalamic patients. The different pattern of results for the valid-cue condition for the thalamic lesion patients, in comparison to that seen with midbrain or parietal lesions, is consistent with a deficit in the engage operation.

The different pattern of experimental results between parietal and thalamic lesion patients is especially interesting when one considers that, even though the thalamic patients had much slower contralesional detection reaction times than parietal patients in the valid-cue condition, most of the parietal lesion patients had more clinical neglect (neglect is defined as a difficulty in reporting targets contralateral to the lesion without any sensory deficit) than did any of the thalamic lesion subjects. The fact that these patients show less clinical neglect than do parietal lesion patients, whose deficit lies in the disengage operation, leads us to speculate that clinical neglect, an important source of disability, can be linked most directly to a disorder in the disengage operation.

It is not possible to make precise inferences about the specific neural structure responsible for the effects found in our patients. In two patients the hemorrhage involved large parts of the thalamus, including the pulvinar, as well as adjacent structures. The most restricted lesion was present in patient NA, who also had the least severe clinical impairment. Since this patient had the same pattern of results as the thalamic group as a whole, both at acute and chronic testing, the anatomic localization of his lesion on CT (Fig. 3) provides the best information on this question. The lesion involves the nuclei lateral posterior, centromedianum, and ventrolateral. Unlike the other two patients, it does not clearly involve the pulvinar (Fig. 3 *Upper*). It extends ventral to the thalamus and involves the perigeniculate region (Fig. 3 *Lower*).

This area may correspond to the region of the perigeniculate nucleus considered by Crick (20) as possibly mediating the "searchlight" of visual attention. This structure, related to the thalamic reticular nuclei, sends γ-aminobutyric acid-secreting projections to the dorsal thalamic nuclei that may gate their processing of sensory information. Petersen *et al.* (14), using the experimental task described here in monkeys, have shown that manipulation of neurotransmission by γ-aminobutyric acid to pulvinar, with iontophoretic injections of muscimol or bicuculline, systematically affects the orienting of attention contralaterally. It would be of interest to compare, in experimental animals, the effects of discrete lesions of pulvinar and of the thalamic reticular region in this task.

Positron emission tomography (PET) scan studies in patients with thalamic lesions show that these lesions produce diffuse hypometabolism throughout the ipsilateral hemisphere (21). These results suggest that the thalamus is involved in cortical activation in some way. Whether such activation can be interpreted in terms of a defect in attention, in the sense applied in this communication, remains conjectural. The hypometabolism (21) was most pronounced in the acute phase and had diminished substantially within 4–6 months.

According to current neurobiological views, the visual cortex involves somewhat separate areas for signal localization and directing of visual attention (parietal) than for pattern recognition (occipitotemporal) (22). We have shown that patients with parietal lesions have defects in pattern recognition on the side contralateral to the lesion (23). This suggests that the ability to recognize patterns rests in part upon an intact visual attention system. The route by which the parietal system interacts with the pattern recognition system is not known. The current results agree with the ideas of others that thalamic nuclei may play a role in this interaction (3, 24). Moreover, it suggests that the thalamic effects on attention are not due to remote effects on cortical or midbrain areas alone. Our evidence is that thalamic lesions produce a different pattern of deficit than that found for midbrain or cortical lesions. Thus, the computations performed by thalamic structures are distinct and do not appear to be an indirect reflection of damage elsewhere. Even closer contact between human studies and alert monkey studies

should be useful in developing a more complete model of how these neural systems interact in orchestrating a shift of visual attention.

This research was supported in part by Contract N-0014-86-0289 from the Office of Naval Research.

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